DATA EVALUATION RECORD

TRIFLUMEZOPYRIM

STUDY TYPE: SUBCHRONIC TOXICITY- RAT
(OCSPP 870.3100)

MRID 49382162

Prepared for

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Task 6-169

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Template version 09/11

TXR#: 0057438

DATA EVALUATION RECORD

STUDY TYPE: 90-Day Oral Toxicity Dietary - Rat;
OCSPP 870.3100 [§82-1a] (rodent); OECD 408.

PC CODE: 129210 **DP BARCODE:** D432127

TEST MATERIAL (PURITY): Triflumezopyrim (99% a.i.)

SYNONYMS: DPX-RAB55, 2,4-Dioxo-1-(5-pyrimidinylmethyl)-3-(3-(trifluoromethyl)-phenyl)-2H-pyrido(1,2-a)pyrimidinium inner salt

CITATION: Papagiannis, C.N. (2015); DPX-RAB55 technical: A 13-week feeding study in rats. DuPont-33960. MPI Research, Mattawan, Michigan. MPI Study No. 125-200. Study date: October 23, 2015. MRID 49382162.

SPONSOR: E.I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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EXECUTIVE SUMMARY:

In a 90-day feeding study, triflumezopyrim was administered to male and female CD®[Crl:CD®(SD)] rats (ten rats/sex/concentration) at concentrations of 0, 100, 400, 1500, and 6000 ppm. The mean daily intakes for male rats were 0, 4.17, 17.01, 63.86, and 257.09 mg/kg bw/day, respectively. The mean daily intakes for female rats were 0, 5.13, 20.38, 74.26, and 278.14 mg/kg bw/day, respectively. Parameters evaluated included body weight, body weight gain, food consumption, food efficiency, clinical signs, hematology, clinical chemistry, urinalysis, ophthalmology, organ weights, and gross or microscopic pathology.

No treatment-related effects were noted on the following parameters: survival, clinical findings, ophthalmoscopic evaluations, coagulation, clinical chemistry, urinalysis, or macroscopic evaluations.

When compared to controls, decreases in mean body weight and food efficiency were observed in males and females at the high dose (6000 ppm). The decrease in food consumption seen at 1500 ppm females was determined to be non-adverse as there was no correlated reduction in absolute body weight or food efficiency.

Hematology effects (mild decreases in red cell mass and eosinophils) were observed in both sexes at 6000 ppm. These effects were not considered to be treatment-related due to the minimal magnitude of effect (generally <10%) and lack of corroborative histopathological changes in relevant organs. Statistically significant organ weight differences were observed at 6000 ppm (minimally increased liver weights in both sexes and increased uterus with cervix weights in females). Based on the magnitude of effect and lack of histopathological

changes in the liver and uterus, these organ weight differences were considered to be non-adverse.

The No-Observed-Adverse-Effect-Level (NOAEL) was 1500 ppm (63.86 mg/kg bw/day in males and 74.26 mg/kg bw/day in females).

The Lowest-Observed-Adverse-Effect-Level (LOAEL) was 6000 ppm (257.09 mg/kg bw/day in males and 278.14 mg/kg bw/day in females) based on decreased absolute body weights in both sexes.

This subchronic oral toxicity study in the rat is classified as **Acceptable / Guideline** and satisfies the requirement for a 90-day oral toxicity study (OCSPP 870.3100; OECD 408) in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Triflumezopyrim technical

Lot/Batch #:	RAB55-104
Purity:	97.04%
Description:	Light yellow solid
CAS #:	1263133-33-0
Stability of test compound:	The test material was stable in feed for at least15 days at room temperature

2. Vehicle: Untreated diet

3. Test animals:

Species:	Rat
Strain:	CD®[Crl:CD®(SD)]
Age at initial dosing:	Approximately 53 days old
Weight at initial dosing:	202-270 g for males; 173-203 g for females
Source:	Charles River Laboratories, Inc., Portage, Michigan.
Acclimation period:	11 days
Diet:	Meal Lab Diet®PMI Nutrition International, LLC Certified Rodent LabDiet® (#5002), *ad libitum*. During the test period, test article was incorporated into the feed of all animals except controls.
Water:	Tap water, *ad libitum*
Housing:	Animals were pair-housed (same sex) in solid bottom caging with nonaromatic bedding and environmental enrichment.

4. Environmental conditions:

Temperature:	20–26°C
Humidity:	30–70%
Air changes:	Not reported
Photoperiod:	Alternating 12-hour light and dark cycles

B. STUDY DESIGN:

1. In-life dates: Start: 7/29/2014; End 10/28/2014

2. Animal assignment: Five groups of ten animals/sex/dose received triflumezopyrim in their diet at concentrations of 0, 100, 400, 1500, or 6000 ppm for 13 weeks. Animals were assigned to dose groups using a standard, by weight, measured value randomization procedure so that there were no statistically significant differences among group body weight means within a sex. A control group received untreated diet. The dietary concentrations were selected by the Sponsor, or in consultation with the Sponsor, on the basis of available data from previous studies.

3. Dose selection rationale: The dietary concentrations were selected based on the findings of a range finding study in male and female Crl:CD(SD) rats. Rats received triflumezo-pyrim in their diet at 0, 200, 800, 4000 or 10,000 ppm for 28 days. The NOAEL was 4000 ppm and the LOAEL was 10,000 ppm based on statistically significant decreases in body weight, body weight gain, food consumption and food efficiency (MRID 49382157).

A new manufacturing process is being used for the test article that has resulted in a different impurity profile for the test article. Therefore, this study serves as a bridging study to the previous 13-week study (DuPont-33960), conducted at the same dietary concentrations.

Table 1. Subchronic Toxicity Study in Rats

Test Group	Concentration in diet (ppm)[a]	Dose to animal (mg/kg bw/day) [b] (Males / Females)	No. of Animals (Males)	No. of Animals (Females)
1	0 (control)	0 / 0	10	10
2	100	4.17 / 5.13	10	10
3	400	17.01 / 20.38	10	10
4	1500	63.86 / 74.26	10	10
5	6000	257.09 / 278.14	10	10

[a] Weight/weight concentration of test article
[b] The dietary concentrations of the test article, Triflumezopyrim, were corrected for 97.04% active ingredient

4. **Diet preparation and analysis:** All test diets were prepared weekly on a weight to weight basis by using a mortar and pestle to grind the premix until uniform in appearance and subsequently blended for 10 minutes using a Hobart mixer. The resulting premix was added to additional meal Lab Diet® and was blended for 20 minutes using a twin shell blender to obtain the appropriate dietary concentrations. All diets were prepared weekly and stored at room temperature. The stability of triflumezopyrim in the dietary mixtures was checked by analysis using HPLC-UV, homogeneity was checked at the beginning of the study, and concentration at 1, 6, and 13 weeks. The test article was at targeted concentrations (±10.5%), homogeneous throughout the feed, and was stable for up to 15 days at room temperature. Based on this information, it can be concluded that the animals received the targeted dietary concentrations of test article during the study.

5. **Statistics:**

Table 2. Statistical Analyses: Subchronic Toxicity Study in Rats

Parameter	Type of Analysis
Body weights Body weight gain Food consumption Hematology (except leukocyte counts) Coagulation Clinical chemistry Organ weights Absolute weights Relative to body and brain weights	Group Pair-wise Comparisons (Levene's/ANOVA-Dunnett's/Welch's
Leukocyte Counts Total leukocyte counts Differential leukocyte counts	Log Transformation/Group Pair-wise Comparisons
Food efficiency Urinalysis Urine volume Specific gravity pH Urine chemistries	Rank Transformation with Dunnett's Test

Results of all pair-wise comparisons were reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

The Reviewer considers the statistical analyses appropriate.

C. METHODS:

1. **Observations:** Animals were observed twice daily for mortality and morbidity and once daily for signs of abnormal behavior and appearance. Once weekly, each animal was individually handled, examined for abnormal behavior and appearance, and subjected to detailed clinical observations.

2. **Body weights:** All animals were weighed once per week.

3. **Food consumption, and compound intake:** Food consumption was measured and recorded weekly during the study. Food consumption was measured for the cage and divided by the number of surviving animals. Food consumption and food efficiency were calculated for each week and month and for the total study duration. If there was a need to exclude food consumption on an individual day (*i.e.* food spillage), weekly food consumption was calculated using an average of acceptable measured food consumption. Compound consumption was calculated for each week that food consumption was measured.

4. **Ophthalmoscopic examinations:** All animals were examined by focal illumination and indirect ophthalmoscopy prior to study start. All surviving animals were examined again prior to scheduled sacrifice.

5. **Hematology and clinical chemistry:** Blood samples were collected from all animals prior to terminal necropsy. Animals were fasted approximately 16 hours prior to sample collection. Evaluation of hematology, clinical chemistry, coagulation, and urinalysis parameters were performed for all animals. Bone marrow smears were collected at scheduled necropsies and retained.

a. Hematology:

Hematocrit (HCT)*	Leukocyte differential count*
Hemoglobin (HGB)*	Mean corpuscular HGB (MCH)*
Leukocyte count (WBC)*	Mean corpuscular. HGB conc.(MCHC)*
Erythrocyte count (RBC)*	Mean corpuscular. volume (MCV)*
Platelet count*	Red cell distribution width
Activated partial thromboplastin time	Automated blood cell morphology
Prothrombin time	

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

b. Clinical chemistry:

ELECTROLYTES	OTHER
Calcium	Albumin*
Chloride	Creatinine*
Phosphorus	Urea nitrogen*
Potassium*	Total Cholesterol*
	Globulins
	Glucose*
ENZYMES (more than 2 hepatic enzymes e.g., *)	Total bilirubin
Alkaline phosphatase (ALK)*	Total protein (TP)*
Alanine aminotransferase (ALT/also SGPT) *	Triglycerides
Aspartate aminotransferase (AST/also SGOT)*	Bile acids

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

c. Urinalysis: Urine samples were collected from all animals prior to terminal necropsy.

Appearance*	Glucose
Volume*	Ketones
Specific gravity/osmolality*	Bilirubin
pH*	Blood/blood cells*
Sediment (microscopic)	Nitrate
Protein*	Urobilinogen

* Optional for 90-day oral rodent studies

6. Sacrifice and Pathology: At termination, animals were sacrificed by isoflurane anesthesia and carbon dioxide inhalation and exsanguinated. Gross examinations were performed on all animals. Organs that were weighed are listed in Table 3. Organ weight/final body weight and organ weight/brain weight ratios were calculated. Tissues collected from animals receiving the highest concentration (6000 ppm) and control (0 ppm) and from one animal that was sacrificed prior to the scheduled sacrifice were processed to slides and evaluated microscopically. Gross lesions and suspected target tissues (heart, kidney, and thyroid), as determined by examination of the control and high concentration animals, were processed to slides and examined microscopically for all animals.

Table 3. Subchronic Toxicity Study in Rats: Organs/tissues collected for pathological examination

	DIGESTIVE SYSTEM	X	CARDIOVASC./HEMAT.	X	NEUROLOGIC
x	Tongue	x	Aorta, thoracic*	x	Brain (multiple sections)*+
x	Salivary glands*	x	Heart*+	x	Periph nerve*
x	Esophagus*	x	Bone marrow[b]*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	x	Spleen*+	x	Eyes (retina, optic nerve)[a]*
x	Jejunum*	x	Thymus*+	**X**	**GLANDULAR**
x	Ileum*			x	Adrenal gland[a]*+
x	Cecum*	**X**	**UROGENITAL**	x	Lacrimal gland[a]
x	Colon*	x	Kidneys[a]*+	x	Parathyroids[a]*
x	Rectum*	x	Urinary bladder*	x	Thyroids[a]*
x	Liver[a]*+	x	Testes[a]*+	**X**	**OTHER**
	Gall bladder (when present)*	x	Epididymides[a]*+	x	Bone (sternum and/or femur)
	Bile duct	x	Prostate[a]*	x	Skeletal muscle
x	Pancreas*	x	Seminal vesicle*	x	Skin*
X	**RESPIRATORY**	x	Ovaries[a]*+	x	All gross lesions and masses*
x	Trachea*	x	Uterus*+	x	Coagulating glands[a],[c]
x	Lung*	x	Mammary gland*	x	Gut associated lymphoid tissue
x	Nose*	x	Ureter[a]		
x	Pharynx*				
x	Larynx*				

* Recommended for 90-day oral studies based on Guideline 870.3100
\+ Organ weighed
[a] Paired organ
[b] Two bone marrow smears were collected at necropsy and held
[c] A combined weight of the seminal vessels and coagulating glands was obtained

II. RESULTS

A. OBSERVATIONS:

1. **Clinical signs of toxicity:** No adverse or test article-related clinical observations were noted at any dietary concentration during the study.

2. **Mortality:** There were no test article-related deaths during the course of this study. One unscheduled euthanasia occurred in the 400 ppm (male) group on study Day 75. The cause of morbidity was peritoneal inflammation and was considered incidental.

B. BODY WEIGHT AND BODY WEIGHT GAIN:

When compared to controls, decreases in mean body weights and body weight gains were observed in males and females at 6000 ppm (Table 4). Body weights of males and females in the 6000 ppm group were statistically significantly lower compared to controls beginning on study Day 7. The statistical significance persisted for most weekly intervals for both sexes. On study Day 91, mean absolute body weight was decreased by 11.0% and 12.3% in males and females, respectively, at 6000 ppm compared with controls (both statistically significant). No statistical significance was noted in any of the other dose groups for weekly mean body weights when compared to controls.

Weekly mean body weight changes were generally lower than control in both sexes at 6000 ppm, with occasional statistically significant decrease. Overall (Days 1-91) mean body change at 6000 ppm was statistically significantly lower than controls by 20% in males and 32% in females (Table 5). No relevant patterns of statistical significance were noted in any of the other dose groups for body weight or body weight changes, when compared to controls, and the few significant changes noted were considered to be incidental variability.

Table 4. Subchronic Toxicity Study in Rats: Body weights (g)

	0 ppm	100 ppm	400 ppm	1500 ppm	6000 ppm
Males					
	0 mg/kg/day	**4.17 mg/kg/day**	**17.01 mg/kg/day**	**63.86 mg/kg/day**	**257.09 mg/kg/day**
Day 1	244.3±11.61	245.2±7.98	243.4±10.04	245.6±11.93	243.0±11.82
Day 91	528.7±44.96	572.5±37.61	555.0±28.28	536.8±50.95	470.6±26.85[a] (-11%)
Females					
	0 mg/kg/day	**5.13 mg/kg/day**	**20.38 mg/kg/day**	**74.26 mg/kg/day**	**278.14 mg/kg/day**
Day 1	186.8±8.50	187.7±7.50	189.3±7.90	187.8±8.61	188.5±7.47
Day 91	314.0±18.73	309.8±20.74	313.9±32.60	301.2±19.31	275.3±13.70[a] (-12%)

[a] Significantly different from control by the Dunnett's Test criteria, $p < 0.01$.

Table 5. Subchronic Toxicity Study in Rats: Body weight gain (g)

Parameter	0 ppm	100 ppm	400 ppm	1500 ppm	6000 ppm
Males					
	0 mg/kg/day	**4.17 mg/kg/day**	**17.01 mg/kg/day**	**63.86 mg/kg/day**	**257.09 mg/kg/day**
Overall body weight gain, Day 1–91	284.4±37.88	327.3±34.66[a]	312.3±30.74	291.2±44.61	227.6±27.65[a] (-20%)
Females					

	0 mg/kg/day	5.13 mg/kg/day	20.38 mg/kg/day	74.26 mg/kg/day	278.14 mg/kg/day
Overall body weight gain, Day 1–91	127.2±15.96	122.1±19.97	124.6±27.47	113.4±13.53	86.8±11.44[a] (-32%)

[a] Significantly different from control by the Dunnett's Test criteria, p <0.01.

C. FOOD CONSUMPTION AND FOOD EFFICIENCY:

When compared to controls, decreases in food intake parameters were observed in both sexes at 6000 ppm and correlated with the body weight effects (Table 6). Statistically significant decreases in weekly mean food consumption were noted for 10 of 13 weeks in males at 6000 ppm (decreases in Weeks 7, 12 and 13, did not reach statistical significance) and for 12 of 13 weeks in females at 6000 ppm (decrease in Week 8 did not reach statistical significance). Statistically significant decreases in mean food consumption were noted for all 3 monthly intervals (Days 1-28, 28-56, and 56-91) in both sexes at 6000 ppm. Overall (Days 1-91) mean food consumption for both sexes at 6000 ppm was statistically lower (decreased 14.4% for males and decreased 24.2% for females) compared to controls. Food consumption was also decreased in females (decreased 15%) only at 1500 ppm compared to controls.

Table 6. Subchronic Toxicity study in rats: Food consumption/food efficiency

Parameter	0 ppm	100 ppm	400 ppm	1500 ppm	6000 ppm
Males					
	0 mg/kg/day	**4.17 mg/kg/day**	**17.01 mg/kg/day**	**63.86 mg/kg/day**	**257.09 mg/kg/day**
Food consumption, (g/animal/day) Day 1-91	23.51	23.84	23.55	22.81	20.13[b] (-14%)
Food efficiency, Day 1–91 (%)	11.51	13.31[a]	12.67	12.38	11.13
Females					
	0 mg/kg/day	**5.13 mg/kg/day**	**20.38 mg/kg/day**	**74.26 mg/kg/day**	**278.14 mg/kg/day**
Food consumption, (g/animal/day) Day 1-91	16.83	15.88	15.99	14.89[b] (-12%)	12.76[b] (-24%)
Food efficiency, Day 1–91 (%)	6.90	6.92	7.17	7.07	7.40

[a] Significantly different from control by the Dunnett's Test criteria, p <0.05.
[b] Significantly different from control by the Dunnett's Test criteria, p <0.01.

D. OPHTHALMOSCOPIC EXAMINATIONS:

No treatment-related ophthalmologic observations were observed at any concentration in either males or females.

E. CLINICAL PATHOLOGY:

1. **Hematology:** Mild test article-related decreases in red cell parameters (erythrocytes, hemoglobin, and hematocrit) and eosinophils were observed in both sexes receiving 6000 ppm (Table 7). Although these differences were statistically significant, they were not considered biologically significant due to the small magnitude of the changes and the values generally remained within historical ranges.

Table 7. Subchronic Toxicity Study in Rats: Hematology findings

Parameter	0 ppm	100 ppm	400 ppm	1500 ppm	6000 ppm
Males (Test Day 92)					
	0 mg/kg/day	**4.17 mg/kg/day**	**17.01 mg/kg/day**	**63.86 mg/kg/day**	**257.09 mg/kg/day**
RBC[a] (10^6/µL)	8.718	8.940	8.588	8.487	8.038[d]
Hb[b] (g/dL)	15.36	15.76	15.44	15.08	14.57[d]
Hematocrit (%)	45.89	47.41	46.12	44.96	43.50[c]
Eosinophils (10^3/µL)	0.132	0.127	0.131	0.094	0.052[d]
Females (Test Day 92)					
	0 mg/kg/day	**5.13 mg/kg/day**	**20.38 mg/kg/day**	**74.26 mg/kg/day**	**278.14 mg/kg/day**
RBC[a] (10^6/µL)	7.934	7.862	7.502[c]	7.513[c]	7.267[d]
Hb[b] (g/dL)	14.42	14.69	14.46	14.08	13.70[c]
Hematocrit (%)	43.03	43.09	42.38	41.47	40.20[d]
Eosinophils (10^3/µL)	0.083	0.095	0.077	0.076	0.032[d]

[a] Red blood cells
[b] Hemoglobin
[c] Significantly different from control by the Dunnett's Test criteria, $p < 0.05$.
[d] Significantly different from control by the Dunnett's Test criteria, $p < 0.01$.

2. **Clinical chemistry:** There were no treatment-related changes in clinical chemistry parameters in male or female rats at any dose level.

3. **Coagulation:** There were no treatment-related changes in coagulation parameters in male or female rats at any dose level.

4. **Urinalysis:** There were no treatment-related alterations in the urinalysis parameters in either sex at any dose level.

F. SACRIFICE AND PATHOLOGY:

1. **Organ weight:** The only test article-related organ weight changes consisted of minimally increased liver weights in males and females at 6000 ppm (statistically significant relative to body weight in males and females, and relative to brain weight in males) and increased uterus with cervix weights in females at 6000 ppm (statistically significant relative to body weight (Table 8). The findings were not considered adverse based on the minimal magnitude of the changes, lack of corresponding liver enzyme changes, and/or the absence of microscopic correlates.

Table 8. Subchronic Toxicity Study in Rats: Organ weights

	0 ppm	100 ppm	400 ppm	1500 ppm	6000 ppm
Males					
	0 mg/kg/day	**4.17 mg/kg/day**	**17.01 mg/kg/day**	**63.86 mg/kg/day**	**257.09 mg/kg/day**
Absolute liver weight (g) (% control)	14.610	16.056 (+9.90)	15.085 (+3.25)	15.256 (+4.42)	16.178 (+10.73)
Relative [a] liver weight (%) (% control)	2.8944	2.9042 (+0.34)	2.8491 (-1.57)	3.0052 (+3.83)	3.5106 (+21.29[c])
Liver to brain weight (%) (% control)	6.7558	7.3918 (+9.41)	7.1339 (+5.60)	7.007 (+3.63)	7.8287 (+15.88[b])
Females					
	0 mg/kg/day	**5.13 mg/kg/day**	**20.38 mg/kg/day**	**74.26 mg/kg/day**	**278.14 mg/kg/day**
Absolute liver weight (g) (% control)	8.567	8.248 (-3.72)	9.337 (+8.99)	8.863 (+3.46)	9.352 (+9.16)
Relative[a] liver weight (%) (% control)	2.9267	2.8536 (-2.50)	3.1774 (+8.57)	3.1649 (+8.14)	3.6821 (+25.81[c])
Liver to brain weight (%) (% control)	4.4633	4.2860 (-3.97)	4.7432 (+6.27)	4.5369 (+1.65)	4.8515 (+8.70)
Absolute uterus with cervix weight (g) (% control)	0.611	0.653 (+6.87)	0.695 (+13.75)	0.708 (+15.88)	0.793 (+29.79)
Relative[a] uterus with cervix weight (%) (% control)	0.2081	0.2262 (+8.70)	0.2365 (+13.65)	0.2534 (+21.77)	0.3121 (+49.98[c])
Uterus with cervix to brain weight (%) (% control)	0.3182	0.3480 (+9.37)	0.3532 (+11.00)	0.3655 (+14.86)	0.4094 (+28.66)

[a] Relative weight is defined as the organ to body weight ratio.
[b] Significantly different from control by the Dunnett's criteria, $p < 0.05$.
[c] Significantly different from control by the Dunnett's criteria, $p < 0.01$.

4. **Gross Pathology:** No treatment-related gross lesions were observed at necropsy.

5. **Histopathology:** There were no treatment-related microscopic findings. All histopathologic observations in this study were consistent with normal background lesions for rats of this age and strain

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATOR'S CONCLUSIONS:

The NOAEL was 1500 ppm (63.86 mg/kg bw/day in males and 74.26 mg/kg bw/day in females) and the LOAEL was 6000 ppm (257.09 mg/kg bw/day in males and 278.14 mg/kg bw/day in females), based on adverse effects on mean body weight and food consumption of both sexes.

B. REVIEWER COMMENTS:

The reviewer agrees with the investigator's interpretation of the findings and the NOAEL and LOAEL established for this study.

The No-Observed-Adverse-Effect-Level (NOAEL) was 1500 ppm (63.86 mg/kg bw/day in males and 74.26 mg/kg bw/day in females).

The Lowest-Observed-Adverse-Effect-Level (LOAEL) was 6000 ppm (257.09 mg/kg bw/day in males and 278.14 mg/kg bw/day in females) based on decreased absolute body weights in both sexes.

C. STUDY DEFICIENCIES:

None